REMARKS

The Office Action of April 18, 2006 presents the examination of claims 1-3 and 5-8. The present paper amends claim 5.

Written description

Claims 1-3 and 5-8 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description support in the specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

In particular, the Examiner asserts that the recitation in the claims that "at least 98% of single polynucleotide polymorphisms are detected" at a level of input genomic DNA of 10 to 40 ng represents "new matter" not previously described in the specification. Applicants disagree.

The Examiner points out that the scope of the claims is such that as many as 10,000, 100,000 or more sites could be typed, with an accuracy of at least 98%, using as little as 10 ng of DNA per 100 sites, noting that there is no upper limit to the number of sites recited in the claims. It appears that the issue is that the claims do not recite any upper limit to the number of sites to be assayed at once.

Applicants submit that the Examiner's own disbelief should not substitute for the affirmative statements of the specification. The Examiner must accept objective statements made in the specification, or else provide some evidence or well-reasoned statement why the Examiner does not believe an assertion made in the specification. See, *e.g. In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

The present invention relates to improvements in multiplex assays for genotyping. The specification provides an example in which 98 of 100 SNP sites are successfully typed using 40 ng of input DNA. The specification also provides an example (Example 4) in which a single site is typed using only 0.1 ng of DNA template, and this example also explains that the multiplexed example (Example 3) may therefore be performed using as little as ¼ the amount (*i.e.* 10 ng per

100 SNP sites) used in Example 3. The specification also alleges that successful typing of, *e.g.* 100,000 sites can be obtained using approximately 10 μg of DNA template (see page 12, line 20).

The Examiner has not provided any evidence or reasoned statement as to why the results of Examples 3 and 4 are not general. Thus, his assertion that the recitation in the claims that 98% success rate in typing in a multiplex assay according to the invention is "new matter" is not persuasive.

The present claims recite a ratio of template DNA consistent with the input ratio of 0.1 ng per SNP site (page 12, lines 21-22) or 10 to 40 ng per 100 SNP sites (Examples 3 and 4). (Claim 5 is amended to limit the number of sites assayed to within this ratio.) Applicants submit that there is adequate written description of the invention as recited in the present claims 1-3 and 5-8, and accordingly the instant rejection should be withdrawn.

Obviousness

Claims 1, 3, 5 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mein et al. in view of Wang et al. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

In particular, the Examiner fails to establish *prima facie* obviousness of the claimed invention. The combined teachings of the references do not disclose or suggest all of the features of the claims; the Examiner provides no reference describing use of an amount of template of about 0.1 ng per SNP site. Neither does the Examiner explain any motivation why such a small amount of DNA template should be used. The Examiner merely relies upon an "optimization" argument to assert that anyone of ordinary skill in the art could arrive at the invention.

At page 10, lines 3-7, the Examiner asserts one of ordinary skill in the art would reasonably expect to extend the success rate of 50% to nearly 100% by "optimization", asserting

that since 558 loci can be typed with 50% success using 100 ng of DNA, it is reasonable to believe one can type half the number of loci with the same amount of DNA and expect nearly a 100% success rate.

Such reasoning is not soundly based. The rate of successful typing is not a linear function of the input DNA amount or the number of loci amplified at once. Rather, failures of the typing assays occur at least partly due to primer dimer formation and annealing of primers to secondary (*i.e.* not the target locus) sites in the genome. The Examiner provides no basis whatsoever for his assumption of a linear correlation between typing error rate and the number of loci typed with a given amount of DNA template.

At the top of page 11 of the Office Action, the Examiner asserts that optimization of a multiplex SNP typing assay is "routine", and at the bottom of page 10 the Examiner quotes the Wang reference, to try to support an allegation of motivation for optimization of the conditions for multiplex reactions, "by grouping them into additional multiplex sets or by redesigning the assays." Neither a general assertion of "optimization", nor the specific approaches to optimization stated by Wang, relates to adjusting the amount of template DNA to the number of sites typed to fall in the range of 10-40 ng per 100 sites. Neither of these approaches to optimization relates to utilizing the TAQMAN or INVADER assays for detection of the polymorphisms. Therefore, where among the myriad parameters of an assay that can be varied during "optimization" is there any suggestion that the ratio of input DNA to number of sites tested is to be adjusted, or that the particular detection methods recited (in claim 1) should be utilized? Applicants assert the answer is "nowhere" and that the Mein and Wang references also fail to make such a suggestion. Therefore the Examiner fails to establish *prima facie* obviousness of the present claims and the rejection of claims 1-3 and 5-8 under 35 U.S.C. § 103(a) over Mein in view of Wang should be withdrawn.

In addition, Applicants submit that the finding that about 0.1 ng of template DNA could be used in combination with the Invader assay to obtain a successful SNP typing rate of $\geq$ 98% (*see*, Example 3 at pp. 18-19 of the specification) is an unexpected result that rebuts any

assertion of *prima facie* obviousness. Therefore, at least claim 1 and claims dependent thereon should be found patentable over the references of record for this additional reason.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Dated: August 1, 2006

Respectfully submitted,

By _____

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